Case Report

Lymphocytic Interstitial Pneumonia Associated with a Marked Increase in Monoclonal IgM-κ-type Rheumatoid Factor and Serum CA19-9

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A 62-year-old Japanese female was admitted due to dyspnea. She showed a marked increase in CA19-9 (maximum, 192,000 U/ml) and monoclonal IgM-κ type rheumatoid factor (RF) activity. The patient died of respiratory failure 3 months later. Autopsy findings revealed an infiltration of IgM-κ-positive plasma cells in the pulmonary interstitium, and therefore a diagnosis of lymphoid interstitial pneumonia (LIP) was made. The bronchoepithelial cells were stained with monoclonal antibody-reactive with CA19-9 antigen. This is the first documented LIP, associated with a marked increase in monoclonal IgM-κ type RF and CA19-9 in the serum.

Key words: Plasma cells, Liver cirrhosis, Immunological disorders

Lymphocytic interstitial pneumonia (LIP) is a primary lymphoreticular disorder affecting the lungs, which is often associated with hyperimmunoglobulinemia or hypogammaglobulinemia (1). Hyperimmunoglobulinemia may be either monoclonal (2) or polyclonal (3). However, no report in the literature has described monoclonal gammaglobulin with rheumatoid factor (RF) activity. CA19-9 is a carbohydrate antigen (4) now widely used as a tumor marker for pancreas cancer. The association of a high titer of CA19-9 with interstitial pneumonia has been rarely reported (5).

We report here a female patient with LIP, associated with a marked increase in monoclonal IgM-κ type RF and serum CA19-9.

CASE REPORT

A 62-year-old woman was admitted to the First Department of Internal Medicine, Kyushu University Hospital, on December 8, 1988, for treatment of dyspnea. She had been well until 13 yrs prior to admission, when exertional dyspnea and dry coughing developed. These symptoms progressively worsened until she consulted a physician two yrs prior to admission. An x-ray film of the chest showed a reticular striation of both lungs and a high titre of CA19-9 (2,100 U/ml) in the serum was found. An ultrasonographic examination of the abdomen showed characteristics of liver cirrhosis with mild splenomegaly, but no abnormality was found in the pancreas. Six months before admission, a flapping tremor and a disordered consciousness developed. Lactulose and neomycin were prescribed for the hepatic encephalopathy which did improve somewhat. The exertional dyspnea persisted unchanged, however, and she was practically bedridden during the three months prior to admission. She had worked in a coal mine for 5 yrs, and later a wool mill for 7 days until she married. She did not smoke and consumed little alcohol. There was no history

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of allergy, arthritis, transfusion, or tuberculosis.

Examination on the day of admission revealed a pulse rate of 72, respiration rate 32, bibasilar crackles, and marked clubbing. No rash, jaundice, lymphadenopathy, hepatosplenomegaly, cyanosis, or signs of arthritis were seen.

Laboratory studies on admission disclosed the following values: hemoglobin, 11.6 g/dl, white cell count 6,600/mm, with 50% neutrophils, 41% lymphocytes, 4% monocytes, and 5% eosinophils; erythrocyte sedimentation rate was 128 mm/l h, and urinalysis was normal. Bone marrow aspiration was of low normal cellularity with no increase of plasma cells. Total bilirubin was 1.1 mg/dl, serum aspartate aminotransferase, 47 U/l, alkaline phosphatase, 200 U/l, total serum proteins, 8.9g/dl with γ-globulin 5.5 g/dl (electrophoresis), IgG 4,800 mg/dl, IgA 1,020 mg/dl, IgM 2,950 mg/dl (immuno-diffusion). The electrophoresis findings showed a polyclonal increase of γ-globulin with M protein, which was identified as IgM-κ by immunofixation.

Serum CA19-9 was markedly elevated to 55,600 U/ml. The titre of carcinoembryonic antigen was slightly high, but the serum amylase, elastase, trypsin and α-fetoprotein were normal. Antinuclear antibody tests were negative, but the titre of immune complex was slightly elevated. Neither hepatitis B surface antigen nor anti-human T lymphocyte-tropic virus type I-antibody was detected. The lymphoblastogenesis of the peripheral lymphocytes by phytohemagglutinin was decreased, and the intradermal purified protein derivative test was negative. The flowcytometry of the peripheral lymphocytes showed a reduced CD4 to CD8 ratio (<1.0). A marked restricted defect was found in the pulmonary function test. The room air arterial blood gas level revealed a PaO₂ of 67.0 mmHg.

The titre of rheumatoid factor (RF) was also extremely high, 1:3.2×10⁵ (RAPA test; normal, <1.40). The isolated RF by affinity chromatography using heat-aggregated rabbit IgG coupled to Sepharose 4B was identified as the M protein (IgM-κ) observed in the serum. Details of monoclonal antibody characteristics will be described elsewhere (6).

A chest x-ray film demonstrated bilateral interstitial reticulonlinear infiltrates (Fig. 1), which were prominent in the right lower lobe where there appeared to be a slight decrease in volume. A ⁶⁷Ga-citrate scintigram revealed a diffuse high uptake in the bilateral lungs. Abdominal CT scanning showed cirrhotic liver with mild splenomegaly without any abnormality in the pancreas. Skeletal x-ray films showed no evidence of osteolytic bone lesions. No biopsy of the lung or bronchoalveolar lavage was performed because of the severe condition of the patient.

The patient was treated with prednisolone, 20 mg/day, from the 60th hospital day. However, the pulmonary lesions progressed, and the hepatic dysfunction also began to deteriorate. The patient died of respiratory failure three months after admission. The serum CA19-9 on the 75th hospital day was 192,000 U/ml.

At autopsy, the lungs showed marked fibrosis with a honeycomb change in the lower lobes. The most remarkable microscopic finding in the lungs was a patchy interstitial infiltrate around the vessels and the bronchioles. The infiltrate was composed predominantly of plasma cells with an admixture of small lymphocytes; the infiltrate lacked any active mitoses (Fig. 2). The hilar lymph nodes showed mild lymphoplasmabiosis, but their structure was well preserved. An immunohistochemical study by the
Fig. 2. Microscopic findings of lower lobes in the autopsied lung. Interstitial infiltration of mononuclear cells of plasma cells with admixed lymphocytes are visible (H.E.; ×180).

Fig. 3. Mature plasma cells show a positive reaction for IgM (arrows). The sections also stained positively for κ light chains. Smaller populations of plasma cells were stained for other classes of immunoglobulins (ABC stain; ×130).

Fig. 4. Some bronchiolar epithelial cells (arrows) and the mucous exudate were positive for CA19-9 (ABC stain; ×150).

avidin-biotin-peroxidase complex (ABC) method disclosed polypytic plasma cells with a predominance of IgM-κ positive cells (Fig. 3), and the diagnosis of lymphoid interstitial pneumonia was made. Another immunohistochemical examination with anti-CA19-9 monoclonal antibody demonstrated an intensely positive reaction of the bronchiolar epithelial cells and the mucous exudate (Fig. 4).

The liver showed marked atrophy and the microscopic findings revealed liver cirrhosis. The spleen was slightly enlarged, but no formation of esophageal varices was seen. The pancreas, cholecystic duct, and gastrointestinal tract were intact, without any malignant lesions.

**DISCUSSION**

Lymphocytic interstitial pneumonia (LIP), first described by Carrington and Liebow (7) in 1966, is the term used for widespread interstitial infiltration of the lung consisting of mature lymphocytes and plasma cells. Microscopically, the infiltrate may be nodular and may be principally accumulated around the bronchi and vessels (8). The number of plasma cells in LIP varies upon the case; a form of LIP rich in plasma cells and associated with hyperglobulinemia has been reported (9).

LIP has been reported in association with a variety of immunological disorders, including Sjögren’s syndrome (10), autoerythrocyte sensitization (8), myasthenia gravis (2), hyper- (1) and hypogammaglobulinemia (11), chronic active hepatitis (1), and recently the acquired immunodeficiency syndrome (12). Thus, LIP is presently thought to be an expression of systemic immunological disorders in the lung. In the present case, the hyperglobulinemia and the anergy to phytohemagglutinin or inversion of the CD4/CD8 ratio of the peripheral lymphocytes support the presence of immunological disorders. In addition, the liver cirrhosis of this patient may also be associated with immunological disorders of LIP.

Hypergammaglobulinemia in LIP is usually polyclonal, but a few cases have been reported to be monoclonal (2, 13). To our knowledge, however, the RF activity of the monoclonal protein associated with LIP has not been reported. In the present case, the M protein was proven to be the IgM-κ type RF, which reacts with the Fc portion of rabbit IgG (6).
Further immunohistochemical study demonstrated that the M protein had originated from the plasma cells which infiltrate the pulmonary interstitium and the hilar lymph nodes. The proliferation of IgM-κ seemed to be a benign monoclonal gammopathy with a polyclonal gammopathy, because additional immunoglobulins also showed an increases but to a lesser extent.

RF is a family of autoantibodies directed against the Fc fragments of IgG (14). It is not confined to patients with rheumatoid arthritis (RA); it is frequently detected in the serum of patients with non-arthritic clinical disorders, particularly those disorders associated with chronic inflammation and infection (15). Furthermore, some studies had indicated that the precursors of IgM RF secreting cells are normal constituents of the B lymphocytes (16, 17). Although the precise role of RF in non-arthritic diseases is not known yet, the following physiological functions have been suggested: augmentation of the binding affinity of the antibody to its antigen (18), amplification of the complement binding (19), increase in the size of immune complexes thereby facilitating their clearance by the reticuloendothelial system (20), regulation of IgG antibody response by interacting with B cell Fc(IgG) receptors or B cell membrane IgG (21). The exact role of the extremely high serum concentration of monoclonal IgM RF in this patient is unclear. At least, the infiltration of IgM RF producing cells in the lung suggests that the RF was produced primarily in the lung area. This may also suggest that some immunologic activation occurring in the lung might have enhanced the production of RF.

Another characteristic finding in the present case is the marked increase of serum CA19-9. CA19-9, one of the gastrointestinal cancer-associated antigens, is defined by the monoclonal antibody which is immunized with a human colon cancer cell line (4). CA19-9 is known to be elevated in the sera of patients with malignancies of the gastrointestinal tract, especially in those who suffer from pancreatic cancer (22). The association of high serum CA19-9 levels and non-malignant diseases, such as pancreatitis (23), choledochitis (24), liver cirrhosis (25), and diabetes mellitus (26) has been also reported. It seems, however, that there have no reports which describe an association of interstitial pneumonia with a marked elevation of CA19-9, with the exception of one report by Okino et al (5). Furthermore, CA19-9 levels in non-malignant diseases are generally lower than in malignant diseases. Dunn and McKinstry reported that the specificity of CA19-9 for pancreas cancer is 99% when the normal upper limit is defined to be 1,000 U/ml (27).

CA19-9 is known to exist in the normal epithelial lining of the biliary tract, gastric mucosa, pancreatic duct and bronchial glands (28). The proportional increase of CA19-9 to the exacerbation of pulmonary lesions and the positive staining for the anti CA19-9 antibody of the bronchial epithelial cells in the present case suggest the significance of the pulmonary lesions as the primary source of CA19-9. Additionally, an elevation of CA19-9 in a patient with idiopathic pulmonary fibrosis has been previously reported (5). Furthermore, the complicated liver cirrhosis in the present case may have promoted the increase of CA19-9 (25). However, the mechanisms of the enhancement of CA19-9 in the bronchoepithelial cells in interstitial pneumonia remain uncertain. A direct association between CA19-9 and the monoclonal RF found in this case is doubtful, because the epitope of CA19-9 is a sialylated Lewisα sugar chain which is not capable of reacting with RF (29). We speculate that an additional factor in the lung may have stimulated the production of the IgM-RF and also may have facilitated the production of CA19-9.

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REFERENCES


